, P

#### SEQUENCE LISTING

<110> De Francesco, Raffaele Tomei, Licia Behrens, Sven-Erik

<120> METHOD FOR REPRODUCING IN VITRO THE
 RNA-DEPENDENT RNA POLYMERASE AND TERMINAL NUCLEOTIDYL
 TRANSFERASE ACTIVITIES ENCODED BY HEPATITIS C VIRUS (HCV)

<130> IT0002PCA <150> 08/952,981 <151> 1998-03-23 <150> PCT/IT96/00106 <151> 1996-05-24 <150> RM95A000343 <151> 1995-05-25 <160> 14 <170> FastSEQ for Windows Version 4.0 <210> 1 <211> 591 <212> PRT <213> Hepatitis C virus Ser Met Ser Tyr Thr Trp Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala 10 5 Glu Glu Ser Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg 3.0 25 20 His His Asn Met Val Tyr Ala Thr Thr Ser Arg Ser Ala Gly Leu Arg 40 45 35 Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Asp His Tyr 55 50 Arg Asp Val Leu Lys Glu Met Lys Ala Lys Ala Ser Thr Val Lys Ala 75 70 Lys Leu Leu Ser Val Glu Glu Ala Cys Lys Leu Thr Pro Pro His Ser 90 95 85 Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser 110 105 100 Ser Lys Ala Val Asn His Ile His Ser Val Trp Lys Asp Leu Leu Glu 125 120 115 Asp Thr Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val 140 135 Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile 155 150 145 Val Phe Pro Asp Leu Gly Val Arg Val Cys Glu Lys Met Ala Leu Tyr 175 170 165 Asp Val Val Ser Thr Leu Pro Gln Val Val Met Gly Ser Ser Tyr Gly 180 185 Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Asn Thr Trp 205 195 200 Lys Ser Lys Lys Asn Pro Met Gly Phe Ser Tyr Asp Thr Arg Cys Phe 220 215 210 Asp Ser Thr Val Thr Glu Asn Asp Ile Arg Val Glu Glu Ser Ile Tyr

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Pro Thr Leu Trp Ala Arg Met Ile Leu Met Thr His Phe Phe Ser Ile
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Gly Ala Cys Tyr Ser Ile Glu Pro Leu Asp Leu Pro Gln Ile Ile Glu
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Arg Leu His Gly Leu Ser Ala Phe Ser Leu His Ser Tyr Ser Pro Gly 465 470 475 480
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Glu Ile Asn Arg Val Ala Ser Cys Leu Arg Lys Leu Gly Val Pro Pro
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Leu Arg Val Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu 500 505 510
Ser Gln Gly Gly Arg Ala Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp 515 520 525
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60

His Val Trp Ile Pro Pro Leu Asn Ala Arg Gly Gly Arg Asp Ala Ile

Ile Leu Leu Met Cys Ala Val His Pro Glu Leu Ile Phe Asp Ile Thr

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Lys Leu Leu Ile Ala Ile Leu Gly Pro Leu Met Val Leu Gln Ala Gly 85 Ile Thr Arg Val Pro Tyr Phe Val Arg Ala Gln Gly Leu Ile His Ala 105 Cys Met Leu Val Arg Lys Val Ala Gly Gly His Tyr Val Gln Met Ala 120 125 Phe Met Lys Leu Gly Ala Leu Thr Gly Thr Tyr Ile Tyr Asn His Leu 135 140 Thr Pro Leu Arg Asp Trp Pro Arg Ala Gly Leu Arg Asp Leu Ala Val 150 155 Ala Val Glu Pro Val Val Phe Ser Asp Met Glu Thr Lys Ile Ile Thr 170 165 Trp Gly Ala Asp Thr Ala Ala Cys Gly Asp Ile Ile Leu Gly Leu Pro
180 185 190 185 Val Ser Ala Arg Arg Gly Lys Glu Ile Leu Leu Gly Pro Ala Asp Ser 195 200 Leu Glu Gly Arg Gly Leu Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ser 215 220 Gln Gln Thr Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly 230 235 Arg Asp Lys Asn Gln Val Glu Gly Glu Val Gln Val Val Ser Thr Ala 245 250 Thr Gln Ser Phe Leu Ala Thr Cys Val Asn Gly Val Cys Trp Thr Val 260 265 270 Tyr His Gly Ala Gly Ser Lys Thr Leu Ala Ala Pro Lys Gly Pro Ile 275 280 285 Thr Gln Met Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Pro Lys 290 295 300 295 Pro Pro Gly Ala Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp 305 310 315 320Leu Tyr Leu Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg 325 330 335 Gly Asp Ser Arg Gly Ser Leu Leu Ser Pro Arg Pro Val Ser Tyr Leu 340 345 350Lys Gly Ser Ser Gly Gly Pro Leu Leu Cys Pro Phe Gly His Ala Val 355 360 365 355 360 Gly Ile Phe Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val 375 380 Asp Phe Val Pro Val Glu Ser Met Glu Thr Thr Met Arg Ser Pro Val 390 395 Phe Thr Asp Asn Ser Ser Pro Pro Ala Val Pro Gln Ser Phe Gln Val 405 410 Ala His Leu His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro
420 425 430 Ala Ala Tyr Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser 435 440 445 Val Ala Ala Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly 455 460 Ile Asp Pro Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ala 470 475 Pro Val Thr Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys 485 490 495485 Ser Gly Gly Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr 500 505 510 Asp Ser Thr Thr Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu 515 520 525 515 Thr Ala Gly Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly 535 540 Ser Val Thr Val Pro His Pro Asn Ile Glu Glu Val Ala Leu Ser Asn 550 555 Thr Gly Glu Ile Pro Phe Tyr Gly Lys Ala Ile Pro Ile Glu Ala Ile 570

Arg Gly Gly Arg His Leu Ile Phe Cys His Ser Lys Lys Cys Asp 580 585 Glu Leu Ala Ala Lys Leu Ser Gly Leu Gly Ile Asn Ala Val Ala Tyr 595 600 605 Tyr Arg Gly Leu Asp Val Ser Val Ile Pro Thr Ile Gly Asp Val Val 610 615 620 Val Val Ala Thr Asp Ala Leu Met Thr Gly Tyr Thr Gly Asp Phe Asp 630 635 Ser Val Ile Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser 645 650 655 Leu Asp Pro Thr Phe Thr Ile Glu Thr Thr Thr Val Pro Gln Asp Ala 660 665 670 Val Ser Arg Ser Gln Arg Arg Gly Arg Thr Gly Arg Gly Arg Gly 675 680 685 Ile Tyr Arg Phe Val Thr Pro Gly Glu Arg Pro Ser Gly Met Phe Asp 700 695 Leu Thr Pro Ala Glu Thr Ser Val Arg Leu Arg Ala Tyr Leu Asn Thr 725  $\phantom{000}735$ 725 730 Pro Gly Leu Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Ser Val 740 745 750 Phe Thr Gly Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys 755 760 765 Gln Ala Gly Asp Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val 770 780 Cys Ala Arg Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys 785 790 795 800 Cys Leu Ile Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu 805 810 815 Tyr Arg Leu Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile 820 825 830 Thr Lys Tyr Ile Met Ala Cys Met Ser Ala Asp Leu Glu Val Val Thr 835 840 845 835 840 Ser Thr Trp Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr 850 860 855 860 Cys Leu Thr Thr Gly Ser Val Val Ile Val Gly Arg Ile Ile Leu Ser 865 870 875 880 Gly Arg Pro Ala Ile Val Pro Asp Arg Glu Leu Leu Tyr Gln Glu Phe 885 890 895 Asp Glu Met Glu Glu Cys Ala Ser His Leu Pro Tyr Ile Glu Gl<br/>p Gly 900 905 910 Met Gln Leu Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln 915 920 925 Thr Ala Thr Lys Gln Ala Glu Ala Ala Ala Pro Val Val Glu Ser Lys 935 940 Trp Arg Ala Leu Glu Thr Phe Trp Ala Lys His Met Trp Asn Phe Ile 950 955 Ser Gly Ile Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro 965 970 Ala Ile Ala Ser Leu Met Ala Phe Thr Ala Ser Ile Thr Ser Pro Leu 980 985 990 980 985 Thr Thr Gln Ser Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala 1000 1005 Ala Gln Leu Ala Pro Pro Ser Ala Ala Ser Ala Phe Val Gly Ala Gly 1020 1010 1015 Ile Ala Gly Ala Ala Val Gly Ser Ile Gly Leu Gly Lys Val Leu Val 1025 1030 1035 104 Asp Ile Leu Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala 1045 1050 1055 Phe Lys Val Met Ser Gly Glu Met Pro Ser Thr Glu Asp Leu Val Asn 1065

x 4 x

Leu Leu Pro Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val 1080 1075 1085 Cys Ala Ala Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val 1095 1100 1090 Gln Trp Met Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val 1105 1110 1115 112 Ser Pro Thr His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr 1125 1130 1135 Gln Ile Leu Ser Ser Leu Thr Ile Thr Gln Leu Leu Lys Arg Leu His 1140 1145 1150 Gln Trp Ile Asn Glu Asp Cys Ser Thr Pro Cys Ser Gly Ser Trp Leu 1165 1155 1160 Arg Asp Val Trp Asp Trp Ile Cys Thr Val Leu Thr Asp Phe Lys Thr 1170 1175 1180Trp Leu Gln Ser Lys Leu Leu Pro Gln Leu Pro Gly Val Pro Phe Phe 1190 1195 Ser Cys Gln Arg Gly Tyr Lys Gly Val Trp Arg Gly Asp Gly Ile Met 1205 1210 1215 1205 1210 1215 Gln Thr Thr Cys Pro Cys Gly Ala Gln Ile Thr Gly His Val Lys Asn 1220 1225 1230 Gly Ser Met Arg Ile Val Gly Pro Lys Thr Cys Ser Asn Thr Trp His 1235 1240 1245 Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Ser 1250 1255 1260 Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu Glu 1265 1270 128 1275 1270 1280 Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly Met 1285 1290 1295 Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu Phe 1300 1305 1310Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala Cys 1315 1320 1325 Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn Gln 1330 1340 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala 1345 1350 1355 136 1360 Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Thr 1365 1370 1375 Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser Ser 1385 1380 1390 Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Thr 1395 1400 1405 His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu Trp 1410 1415 1420

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1700 1705 1710

Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser Ser Lys Ala Val Asn His
1715 1720 1725 Ile His Ser Val Trp Lys Asp Leu Leu Glu Asp Thr Val Thr Pro Ile 1730 1735 1740 Asp Thr Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu 1745 1750 1755 1760 Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly 1765 1770 1775 Val Arg Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Thr Leu 1780 1785 1790

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1940 1945 1950 Met Thr Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr 1955 1960 1965 Asp Leu Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His 1970 1975 1980 Asp Ala Ser Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr 1985 1990 1995 200 2000 Pro Leu Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn 2005 2010 2015 Ser Trp Leu Gly Asn Ile Ile Met Tyr Ala Pro Thr Leu Trp Ala Arg 2020 2025 2030 Met Ile Leu Met Thr His Phe Phe Ser Ile Leu Leu Ala Gln Glu Gln 2035 2040 2045 Leu Glu Lys Ala Leu Asp Cys Gln Ile Tyr Gly Ala Cys Tyr Ser Ile 2055 2060

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Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Leu Ser Arg 2165 2170 2175	
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#### SEQUENCE LISTING GENERAL INFORMATION (i) APPLICANT: ISTITUTO DI RICERCHE DI BIOLOGIA MOLECOLARE P. ANGELETTI S.p.A. 5 (ii) TITLE OF INVENTION: METHOD FOR REPRODUCING IN VITRO THE RNA-DEPENDENT RNA POLYMERASE AND TERMINAL NUCLEOTIDYL TRANSFERASE ACTIVITIES ENCODED BY HEPATITIS C VIRUS (HCV) 10 (iii) NUMBER OF SEQUENCES: 14 (iv) CORRESPONDENCE ADDRESS: (A) ADDRESSEE: Societa Italiana Brevetti (B) STREET: Piazza di Pietra, 39 (C) CITY: Rome 15 (D) COUNTRY: Italy (E) POSTAL CODE: 1-00186 COMPUTER READABLE FORM: (V) (A) MEDIUM TYPE: Floppy disk 3.5" 1.44 **MBYTES** 20 (B) COMPUTER: IBM PC compatible (C) OPERATING SYSTEM: PC-DOS/MS-DOS Rev. 6.22 (D) SOFTWARE: Microsoft Word 6.0 (viii) ATTORNEY INFORMATION (A) NAME: DI CERBO, Mario (Dr.) 25 (C) REFERENCE: RM/X88530/PCT-DC (ix) TELECOMMUNICATION INFORMATION (A) TELEPHONE: 06/6785941 (B) TELEFAX: 06/6794692 (C) TELEX: 612287 ROPAT 30 (1) INFORMATION FOR SEQ ID NO: 1: SEQUENCE CHARACTERISTICS (i) (A) LENGTH: 591 amino acids (B) TYPE: amino acid 35 (C) STRANDEDNESS: single

### SUBSTITUTE SHEET (RULE 26)

(D) TOPOLOGY: linear

MOLECULE TYPE: protein

(ii)

(iii)	HYPOTHETICAL:	No
(iv)	ANTISENSE:	No

(v) FRAGMENT TYPE: C-terminal fragment

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- (vi) ORIGINAL SOURCE:
- 5 (A) ORGANISM: Hepatitis C Virus
  - (C) ISOLATE : BK
  - (vii) IMMEDIATE SOURCE: cDNA clone pCD(38-9.4)
     described by Tomei et al. 1993
  - (ix) FEATURE:
- 10 (A) NAME: NS5B Non-structural polyprotein (C) IDENTIFICATION METHOD: Experimentally
  - (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1: Ser Met Ser Tyr Thr Trp Thr Gly Ala Leu Ile Thr Pro Cys Ala Ala
- 1 5 10 15 15 Glu Glu Ser Lys Leu Pro Ile Asn Ala Leu Ser Asn Ser Leu Leu Arg
- 20 25 30

  His His Asp Met Val Tyr Ala Thr Thr Sor Arg Son Ala Chu Leu Ang
  - His His Asn Met Val Tyr Ala Thr Thr Ser Arg Ser Ala Gly Leu Arg

    35 40 45
- Gln Lys Lys Val Thr Phe Asp Arg Leu Gln Val Leu Asp Asp His Tyr 20 50 55 60
  - Arg Asp Val Leu Lys Glu Met Lys Ala Lys Ala Ser Thr Val Lys Ala 65 70 75 80
  - Lys Leu Leu Ser Val Glu Glu Ala Cys Lys Leu Thr Pro Pro His Ser
- 25 Ala Lys Ser Lys Phe Gly Tyr Gly Ala Lys Asp Val Arg Asn Leu Ser 100 105 110
  - Ser Lys Ala Val Asn His Ile His Ser Val Trp Lys Asp Leu Leu Glu
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- Asp Thr Val Thr Pro Ile Asp Thr Thr Ile Met Ala Lys Asn Glu Val
  - Phe Cys Val Gln Pro Glu Lys Gly Gly Arg Lys Pro Ala Arg Leu Ile

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Phe Gln Tyr Ser Pro Gly Gln Arg Val Glu Phe Leu Val Asn Thr Trp

200

195

-25-

205

	Lys	Ser	Lys	Lys	Asn	Pro	Met	Gly	Phe	Ser	Tyr	Asp	Thr	Arg	Cys	Phe
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	Val	Val	Ile	Cys	Glu	Ser	Ala	Gly	Thr	Gln	Glu	Asp	Ala	Ala	Ser	Leu
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	Arg	Val	Phe	Thr	Glu	Ala	Met	Thr	Arg	Tyr	Ser	Ala	Pro	Pro	Gly	Asp
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	Pro	Pro	Gln	Pro	Glu	Tyr	Asp	Leu	Glu	Leu	Ile	Thr	Ser	Cys	Ser	Ser
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	Asn	Val	Ser	Val	Ala	His	Asp	Ala	Ser	Gly	Lys	Arg	Val	Tyr	Tyr	Leu
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	Arg	His	Thr	Pro	Val	Asn	Ser	Trp	Leu	Gly	Asn	Ile	Ile	Met	Tyr	Ala
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	Pro	Thr	Leu	Trp	Ala	Arg	Met	Ile	Leu	Met	Thr	His	Phe	Phe	Ser	Ile
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	Gly	Ala	Cys	Tyr	Ser	Ile	Glu	Pro	Leu	Asp	Leu	Pro	Gln	Ile	Ile	Glu
		450					455					460				
35	Arg	Leu	His	Gly	Leu		Ala	Phe	Ser	Leu		Ser	Tyr	Ser	Pro	
	465					470					475					480
	Glu	Ile	Asn	Arg	Val	Ala	Ser	Cys	Leu	Arg	Lys	Leu	Gly	Val	Pro	Pro

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And the control of th

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Leu Arg Val Trp Arg His Arg Ala Arg Ser Val Arg Ala Arg Leu Leu 500 505 5 Ser Gln Gly Gly Arg Ala Ala Thr Cys Gly Lys Tyr Leu Phe Asn Trp 520 Ala Val Lys Thr Lys Leu Lys Leu Thr Pro Ile Pro Ala Ala Ser Arg 530 535 Leu Asp Leu Ser Gly Trp Phe Val Ala Gly Tyr Ser Gly Gly Asp Ile 10 550 Tyr His Ser Leu Ser Arg Ala Arg Pro Arg Trp Phe Met Leu Cys Leu 565 570 Leu Leu Ser Val Gly Val Gly Ile Tyr Leu Leu Pro Asn Arg 580 585 590 15 (2) INFORMATION FOR SEQ ID NO: 2: (i) SEQUENCE CHARACTERISTICS (A) LENGTH: 2201 amino acids (B) TYPE: amino acid 20 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: polypeptide (iii) HYPOTHETICAL: No (iv) ANTISENSE: No 25 FRAGMENT TYPE: C-terminal fragment (V) (vii) IMMEDIATE SOURCE: cDNA clone pCD(38-9.4) described by Tomei et al. 1993 (ix) FEATURE: (A) NAME: NS2-NS5B Nonstructural Protein 30 Precursor (C) IDENTIFICATION METHOD: Experimentally (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2: Met Asp Arg Glu Met Ala Ala Ser Cys Gly Gly Ala Val Phe Val Gly

### SUBSTITUTE SHEET (RULE 26)

Leu Val Leu Leu Thr Leu Ser Pro Tyr Tyr Lys Val Phe Leu Ala Arg 25

Leu Ile Trp Trp Leu Gln Tyr Phe Thr Thr Arg Ala Glu Ala Asp Leu

10

-27-

			35					40					45			
	His	Val	Trp	Ile	Pro	Pro	Leu	Asn	Ala	Arg	Gly	Gly	Arg	Asp	Ala	Ile
		50					55					60				
	Ile	Leu	Leu	Met	Cys	Ala	Va1	His	Pro	Glu	Leu	Ile	Phe	Asp	Ile	Thr
5	65					70					75					80
	Lys	Leu	Leu	Ile	Ala	Ile	Leu	Gly	Pro	Leu	Met	Val	Leu	Gln	Ala	Gly
					85					90					95	`
	Ile	Thr	Arg	Val	Pro	Tyr	Phe	Val	Arg	Ala	Gln	Gly	Leu	Ile	His	Ala
				100					105					110		
10	Cys	Met	Leu	Val	Arg	Lys	Val	Ala	Gly	Gly	His	Tyr	Val	Gln	Met	Ala
			115					120					125			
	Phe	Met	Lys	Leu	Gly	Ala	Leu	Thr	Gly	Thr	Tyr	Ile	Tyr	Asn	His	Leu
		130					135					140				
	Thr	Pro	Leu	Arg	Asp	Trp	Pro	Arg	Ala	Gly	Leu	Arg	Asp	Leu	Ala	Val
15	145					150					155					160
	Ala	Val	Glu	Pro	Val	Val	Phe	Ser	Asp	Met	Glu	Thr	Lys	Ile	Ile	Thr
					165					170					175	
	Trp	Gly	Ala		Thr	Ala	Ala	Cys	Gly	Asp	Ile	Ile	Leu	Gly	Leu	Pro
20		_		180					185					190		
20	Val	Ser		Arg	Arg	Gly	Lys		Ile	Leu	Leu	Gly		Ala	Asp	Ser
			195					200					205			
	Leu	Glu	Gly	Arg	Gly	Leu		Leu	Leu	Ala	Pro		Thr	Ala	Tyr	Ser
	a1 -	210	<b>m</b> 1	•	<b>~</b> 3		215	-1	_			220		_		
25	225	Gln	Thr	Arg	GIĀ		ren	СТĀ	Cys	Ile		Thr	Ser	Leu	Thr	
2.5		Acn	7 170	n en	Cl n	230	C1	c1	C1	17- 3	235	3/- 1	37- 3	c	<b>~</b>	240
	ALG	Asp	пуз	Maii	245	val	GIU	GIY	GIU	250	GIN	vaı	Val	ser	255	AIA
	Thr	Gln	Ser	Phe		Δla	Thr	Cve	Val		G1 to	Va I	Ctre	Trn		V=1
				260	#Cu	71111	1	Cys	265	voii	GLY	Val	Cys	270	1111	Val
30	ጥህሥ	His	Glv		G1 v	Ser	T.ve	ሞኩ፦		בומ	Δ1 =	Dro	Tue		Dro	Tla
	+ y -		275		CTY	501	Lys	280	neu	A.a	ALG	FLO	285	Gry	- 10	TTE
	Thr	Gln		Tvr	Thr	Asn	Val		Gln	Asp	Leu	Val		Trp	Pro	Lvs
		290		-			295	•				300	4			-4-
	Pro	Pro	Gly	Ala	Arg	Ser	Leu	Thr	Pro	Cvs	Thr		Gly	Ser	Ser	Asp
35	305		-		-	310				•	315	-	•			320
	Leu	Tyr	Leu	Val	Thr	Arg	His	Ala	Asp	Val		Pro	Val	Arg	Arg	Arg
		•			325	190			-	330				-	335	-

-28-

	GT.	Asţ	Ser	Arq	g Gly	' Ser	: Let	ı Lev	Ser	Pro	Arç	Pro	Val	. Ser	Ту	. Leu
				340	)		•		345	5				350	l	
	Lys	Gly	Ser	Ser	Gly	Giy	Pro	Leu	Leu	Cys	Pro	Phe	Gly	/ His	Ala	ı Val
5			355	5				360	1				365	i		
	Gly	' Ile	Phe	Arg	, Ala	Ala	. Val	Cys	Thr	Arg	Gly	Val	. Ala	Lys	Ala	Val
•		370					375	,				380	1			
	Asp	Phe	Val	Pro	Val	Glu	Ser	Met	Glu	Thr	Thr	Met	Arg	Ser	Pro	Val
	385					390					395					400
10	Phe	Thr	Asp	Asn	Ser	Ser	Pro	Pro	Ala	Val	Pro	Gln	Ser	Phe	Gln	Val
					405					410					415	
	Ala	His	Leu	His	Ala	Pro	Thr	Gly	Ser	Gly	Lys	Ser	Thr	Lys	Val	Pro
				420					425					430		
	Ala	Ala	Tyr	Ala	Ala	Gln	Gly	Tyr	Lys	Val	Leu	Val	Leu	Asn	Pro	Ser
15			435					440					445			
	Val		Ala	Thr	Leu	Gly	Phe	Gly	Ala	Tyr	Met	Ser	Lys	Ala	His	Gly
		450					455					460				
		Asp	Pro	Asn	Ile		Thr	Gly	Val	Arg	Thr	Ile	Thr	Thr	Gly	Ala
	465					470					475					480
20	Pro	Val	Thr	Tyr	Ser	Thr	Tyr	Gly	Lys	Phe	Leu	Ala	Asp	Gly	Gly	Cys
	_				485					490					495	
	Ser	Gly	Gly		Tyr	Asp	Ile	Ile		Cys	Asp	Glu	Cys	His	Ser	Thr
	2	0	m1	500	- 1	_			505					510		
25	Asp	ser		Thr	Ile	Leu	GTA		Gly	Thr	Val	Leu		Gln	Ala	Glu
23	Th.	71-	515	71 -	<b>.</b>	•	••- •	520	_				525	_	_	
	1111	530	GTĀ	ALA	Arg	Leu		Val	Leu	Ala	Thr		Thr	Pro	Pro	Gly
	Ser		Th r	Val	Dro		535	<b>7</b> ~ ~	<b>7</b> 1.	G1	G1	540	21-	<b>.</b>		_
	545	447	1111	Val	Pro	550	FIG	ASII	TTE	Giu	555	val	ATA	Leu	ser	
30		Glv	Glu	Tla	Pro		Tur	GI v	T	7.1.0		D=-	T1_	C1	n 3 -	560
	••••	G.T.Y	GIU	116	565	FIIG	TĀT	GIY	пĀг	570	TTE	PIO	TTE	GIU		IIe
	Ara	Glv	Glv	Δτα	His	T.e.11	Tle	Pha	Cvc		505	T	T 110	T	575	3
	9	1	,	580				1110	585	112.5	Jer	дуз	пуз	590	Cys	ASP
	Glu	Leu	Ala		Lys	Len	Ser	Glv		G1 17	T1_	Aen	Δ1 a		Δla	m
35			595		-,-		~~=	600		<u>y</u>	***		605		a	тĀТ
	Tyr	Ara		Leu	Asp	Val	Ser		Ile	Pro	ፓስ r	Ile		Asn	Va 1	٧a١
	-	610	- 4				615					620	1	P		

-29-

	Val	Val	Ala	Thr	Asp	Ala	Leu	Met	Thr	Gly	Tyr	Thr	Gly	Asp	Phe	Asp
	625					630					635					640
_	Ser	Val	Ile	Asp		Asn	Thr	Cys	Val	Thr	Gln	Thr	Val	Asp	Phe	Ser
5					645					650					655	
	Leu	Asp	Pro			Thr	Ile	Glu		Thr	Thr	Val	Pro		Asp	Ala
				660					665					670		
	Val	Ser		Ser	Gln	Arg	Arg		Arg	Thr	Gly	Arg	Gly	Arg	Arg	Gly
1.0		_	675					680					685			
10	Ile		Arg	Phe	Val	Thr		Gly	Glu	Arg	Pro		Gly	Met	Phe	Asp
		690					695					700				
		Ser	Val	Leu	Cys		Cys	Tyr	Asp	Ala	Gly	Cys	Ala	Trp	Tyr	Glu
	705		_			710					715					720
1 5	Leu	Thr	Pro	Ala		Thr	Ser	Val	Arg	Leu	Arg	Ala	Tyr	Leu	Asn	Thr
15		-1	_	_	725	_				730					735	
	Pro	GIY	Leu		Val	Cys	Gln	Asp		Leu	Glu	Phe	Trp		Ser	Val
	<b>D</b> 1	<b>~</b> 1		740					745					750		
	rne	Thr		Leu	Thr	His	Ile		Ala	His	Phe	Leu		Gln	Thr	Lys
20	<b>~</b> 3		755	_	_		_	760	_				765			
20	GIN		GIŸ	Asp	Asn	Phe		Tyr	Leu	Val	Ala		Gln	Ala	Thr	Val
	~	770	<b>3</b>		<b></b>		775	_	_	_	_	780				
	785	MIA	Arg	Ата	GIN		Pro	Pro	Pro	Ser		Asp	GIn	Met	Trp	
		T 011	T10	7	T 0	790	D==	mr	7	***	795	5	<b></b>		_	800
25	Cys	Deu	116	Arg	805	гÀг	PIO	inr	Leu	His	GIĀ	Pro	Tnr	Pro		Leu
	<b>ጥ</b> ኒታዮ	Ara	T.611	G1 v		V-1	C1 n	7.00	C1	810 Val	#T la	T	m	***	815	<b>T</b> 1-
	- <u>y -</u>	11119	nea	820	n.a	Val	GIII	ASII	825	AST	Inf	Leu	THE	830	PIO	TIE
	ጥት r	Tare	ጥተንም		Ma+	7 l s	Circ	Mat.		Ala	N = m	T	~1		17-1	mь
		2,5	835		ricc	n.u	Cys	840	Ser	Λια	vsh	nea	845	val	Val	IIIL
30	Ser	Thr		Val	Leu	Val	Glv		Val	Leu	Δla	Δla		ΔΙα	Δla	Tur
		850					855	1	• • • •			860		7	,,,,,	- 7 -
	Cys		Thr	Thr	Gly	Ser		Val	Ile	Val	Glv		Ile	Ile	Leu	Ser
	865				• .	870					875	5				880
		Arg	Pro	Ala	Ile		Pro	Asp	Arg	Glu		Leu	Tyr	Gln	Glu	
35	-	-			885			•	•	890		• • •	4		895	
	Asp	Glu	Met	Glu	Glu	Cys	Ala	Ser	His	Leu	Pro	Tyr	Ile	Glu		Glv
	-			900		-			905			<b>-</b> -	,	910		4

-30-

	Met	Gln	Leu 915		. Glu	Glr	n Phe	920		ı Lys	s Alá	a Leu	925		. Leu	Gln
5	Thr	Ala 930	Thr	Lys	Gln	Ala	Glu 935		a Ala	a Ala	Pro	Val 940		Glu	. Ser	Lys
	Trp	Arg	Ala	Leu	Glu	Thr	Phe	Trp	Ala	Lys	His	Met	Trp	Asn	. Phe	Ile
	945					950					955	<b>;</b>				960
	Ser	Gly	Ile	Gln	Tyr	Leu	Ala	Gly	Leu	Ser	Thr	Leu	Pro	Gly	Asn	Pro
					965					970					975	
10	Ala	Ile	Ala	Ser	Leu	Met	Ala	Phe	Thr	Ala	Ser	Ile	Thr	Ser	Pro	Leu
				980					985					990		
	Thr	Thr		Ser	Thr	Leu				Ile	Leu	Gly	Gly	Trp	Val	Ala
	21-	<b>6</b> 1	995		_			1000					1005			
15	Ala		Leu	Ala	Pro			Ala	Ala	Ser			Val	Gly	Ala	Gly
13		.010	G1 ··	21-	21-		1015					1020				
	Ile 1025		GTĀ	MIA		Vai 1030	GTĀ	ser	TTE			Gly	Lys	Val		
	Asp		T.em	Δ1 a			G1 v	71-	C1		1035			_		.040
					L045	- y -	GLY	vra		1050	ATA	GŢĀ	Ala		Val 1055	ALa
20	Phe	Lys	Val			Gly	Glu	Met			Thr	Glu	Asp			Aen
				.060					1065					1070		
	Leu	Leu	Pro	Ala	Ilė	Leu	Ser	Pro	Gly	Ala	Leu	Val	Val	Gly	Val	Val
			075					1080					.085			
	Cys :	Ala .	Ala	Ile	Leu	Arg	Arg	His	Val	Gly	Pro	Gly	Glu	Gly	Ala	Val
25	1	090				1	.095				1	100				
	Gln '	Trp	Met	Asn	Arg	Leu	Ile	Ala	Phe	Ala	Ser	Arg	Gly	Asn	His	Val
	1105					110					.115					120
	Ser 1	Pro '	Thr			Val	Pro	Glu			Ala	Ala	Ala	Arg	Val	Thr
30	Clm 1	r1 ·	<b>.</b>		125	-				.130					135	
50	Gln ]	LI <del>e</del> .		Ser 140	ser	Leu	Thr			Gln	Leu	Leu			Leu :	His
	Gln 7	rn '			c1,,	A en	Cue		145	Dwa	C	C		150	<b></b> .	
			155		<b>01</b> 4 .	nsp		160	IIII	PIO	cys		GIY 165	ser	Trp .	Leu
	Arg A			Tro .	Asp '	Fro			Thr	Va 1	Leu			Dha '	****	n 1
35		170					175	-,5		· a.i.		180	nap	ene .	⊔ys :	ınr
	Trp I		Gln :	Ser :	Lys I			Pro	Gln	Leu			Val	Pro 1	Phe :	?he
	1185					190					195	4	_			200

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Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly  1285 1290 1295  Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu  15 1300 1305 1310  Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala  1315 1320 1325  Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn  1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val  1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser  1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu  1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp (  1445 1450 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro		Ser Cys	Gln Ar	g Gly 1	Tyr Lys	Gly	Val	Trp	Arg	Gly	Asp	Gly	Ile	Met
S				1205		•		1210					1215	
S														
Gly Ser Met Arg Ile Val Gly Pro Lys Thr Cys Ser Asn Thr Trp  1235 1240 1245 Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro 1250 1255 1260  10 Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu 1265 1270 1275 Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly 1285 1290 1295 Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu 1300 1305 1310 Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala 1315 1320 1325 Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1 Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 1390 Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405 His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420 30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1450 1455 Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1445 1450 1460 1465 1470 Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		Gln Thr	Thr Cys	Pro C	Cys Gly	Ala	Gln	Ile	Thr	Gly	His	Val	Lys	Asn
1235   1240   1245	5		1220	)		:	1225					1230		
Gly Thr Phe Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro 1250 1255 1260  10 Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu 1265 1270 1275 1  Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly 1285 1290 1295  Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu 15 1300 1305 1310  Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala 1315 1320 1325  Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 25 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp (1445 1450 1455)  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1  1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Fro Pro		Gly Ser	Met Ar	J Ile V	/al Gly	Pro	Lys	Thr	Cys	Ser	Asn	Thr	Trp	His
1250 1255 1260  Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu 1265 1270 1275 1  Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly 1285 1290 1295  Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu 1300 1305 1310  Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala 1315 1320 1325  Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro			1235			1240					1245			
10 Pro Ala Pro Asn Tyr Ser Arg Ala Leu Trp Arg Val Ala Ala Glu 1265 1270 1275 1 Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly 1285 1290 1295 Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu 1300 1305 1310 Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala 1315 1320 1325 Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340 20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1 Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375 Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 25 1380 1385 1390 Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405 His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420 30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1 Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp (  1445 1450 1450 1455 Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1 Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1 Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1 Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1 Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1 Arg Clu Val Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro Pro Pro Pro Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro		Gly Thr	Phe Pro	Ile A	Asn Ala	Tyr	Thr	Thr	Gly	Pro	Cys	Thr	Pro	Ser
1265 1270 1275 1  Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly 1285 1290 1295  Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu 1300 1305 1310  Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala 1315 1320 1325  Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 64  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Fro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro		1250			1255				;	1260				
Tyr Val Glu Val Thr Arg Val Gly Asp Phe His Tyr Val Thr Gly  1285 1290 1295  Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu 1300 1305 1310  Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala 1315 1320 1325  Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1 Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 25 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1450 1455  Arg Glu Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp Glu Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp Glu Clu Asp Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 35 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro	10	Pro Ala	Pro Asr	Tyr S	er Arg	Ala	Leu	Trp	Arg	Val	Ala	Ala	Glu	Glu
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu  15		1265		12	70			3	1275			•	3	1280
Thr Thr Asp Asn Val Lys Cys Pro Cys Gln Val Pro Ala Pro Glu  1300 1305 1310  Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala  1315 1320 1325  Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn  1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val  1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser  1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu  1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp  1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys  1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		Tyr Val	Glu Val	. Thr A	rg Val	Gly	Asp	Phe	His	Tyr	Val	Thr	Gly	Met
15				1285			1	1290				1	1295	
Phe Ser Glu Val Asp Gly Val Arg Leu His Arg Tyr Ala Pro Ala  1315 1320 1325  Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 25 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Ala Glu Glu Asp 1445 145 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		Thr Thr	Asp Asr	Val L	ys Cys	Pro	Cys	Gln	Val	Pro	Ala	Pro	Glu	Phe
Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Ala Glu Glu Asp (  1445 1450 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro	15		1300	1		1	1305				:	1310		
Arg Pro Leu Leu Arg Glu Glu Val Thr Phe Gln Val Gly Leu Asn 1330 1335 1340  20 Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1 Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 25 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Ala Glu Glu Asp 1 145 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		Phe Ser	Glu Val	Asp G	ly Val	Arg	Leu	His	Arg	Tyr	Ala	Pro	Ala	Cys
1330 1335 1340  Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1  Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 135 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro 150			1315		;	1320				1	L325			
Tyr Leu Val Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val 1345 1350 1355 1 Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu 1365 1370 1375 Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser 25 1380 1385 1390 Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405 His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420 30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1 Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 145 1460 1465 1470 Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		Arg Pro	Leu Leu	Arg G	lu Glu	Val	Thr	Phe	Gln	Val	Gly	Leu	Asn	Gln
1345  1350  1355  1 Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  1365  1370  1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser  25  1380  1385  1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  1395  1400  1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu  1410  1415  1420  30  Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  1425  1430  1435  1445  1450  1455  Arg Glu Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp  1445  1450  1460  1465  1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		1330			1335				1	L <b>34</b> 0				
Val Leu Thr Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu  1365 1370 1375  Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser  1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu  1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp  1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys  35 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro	20	Tyr Leu	Val Gly	Ser G	ln Leu	Pro	Cys	Glu	Pro	Glu	Pro	Asp	Val	Ala
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser  1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr 1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro														360
Ala Lys Arg Arg Leu Ala Arg Gly Ser Pro Pro Ser Leu Ala Ser  1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 35 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		Val Leu			eu Thr	Asp	Pro	Ser	His	Ile	Thr	Ala	Glu	Thr
25 1380 1385 1390  Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu  1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn  1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp  1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys  35 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro														
Ser Ala Ser Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr  1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1 Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro	25	Ala Lys			la Arg			Pro	Pro	Ser	Leu	Ala	Ser	Ser
1395 1400 1405  His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu 1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro 1450 1450 1450 1450 1450 1450 1450 1450	25				_									
His His Val Ser Pro Asp Ala Asp Leu Ile Glu Ala Asn Leu Leu  1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1 Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro				Leu S			Ser	Leu	Lys			Cys	Thr	Thr
1410 1415 1420  30 Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro 1465 1460 1465 1470				D 3			<b>.</b>	~ 1	~1			_	_	_
Arg Gln Glu Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn 1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro 1			val Ser	PIO A		Asp	ren	TTE			Asn	Leu	Leu	Trp
1425 1430 1435 1  Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro 1465 1460 1465 1470	30		Glu Met	Glw G		T10	mh =	7 ~~			C	C1	2	<b>.</b>
Val Val Val Leu Asp Ser Phe Asp Pro Leu Arg Ala Glu Glu Asp 1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro 1			GIU MEC			116	1111			GIU	ser	GIU.		_
1445 1450 1455  Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys :  1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro			Val Len			Aen	Pro			Δla	G1.,	Glu		440
Arg Glu Val Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Lys Lys 35  1460  1465  1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro 3		,41 ,41			or the	nsp			ALG	ALG	GIU		-	GIU
35 1460 1465 1470  Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro		Ara Glu			ro Ala	Glu			Δτα	T.vs	Ser			Dho
Pro Ala Ala Met Pro Ile Trp Ala Arg Pro Asp Tyr Asn Pro Pro	35								9	-,-			~y ~	- 116
		Pro Ala		Pro I	le Tro			Pro .	Asp	Tyr			Pro	Leu
140U 1480			1475			480	,		•		485		- '	_

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	Leu Glu	Ser	Trp Lys	Asp	Pro	Asp	Tyr	Val	Pro	Pro	Val	Val	His	Gly
	1490			:	1495				;	1500				
	Cys Pro	Leu	Pro Pro	ile	Lys	Ala	Pro	Pro	Ile	Pro	Pro	Pro	Arg	Arg
5	1505			1510				:	1515					1520
	Lys Arg	Thr	Val Val	Leu	Thr	Glu	Ser	Ser	Val	Ser	Ser	Ala	Leu	Ala
			1525				:	1530				;	1535	
	Glu Leu	Ala	Thr Lys	Thr	Phe	Gly	Ser	Ser	Glu	Ser	Ser	Ala	Val	Asp
		1	.540			:	1545					1550		
10	ser Gly	Thr	Ala Thr	Ala	Leu	Pro	Asp	Gln	Ala	Ser	Asp	Asp	Gly	Asp
	:	1555			1	.560					1565			
	Lys Gly	Ser	Asp Val	Glu	Ser	Tyr	Ser	Ser	Met	Pro	Pro	Leu	Glu	Gly
	1570			:	1575				1	1580				
	Glu Pro	Gly	Asp Pro	Asp	Leu	Ser	Asp	Gly	Ser	Trp	Ser	Thr	Val	Ser
15	1585		:	1590				1	L595				=	1600
	Glu Glu	Ala	Ser Glu	Asp	Val	Val	Cys	Cys	Ser	Met	Ser	Tyr	Thr	Trp
			1605				:	1610				3	1615	
	Thr Gly	Ala	Leu Ile	Thr	Pro	Cys	Ala	Ala	Glu	Glu	Ser	Lys	Leu	Pro
		1	.620			1	1625				:	L <b>63</b> 0		
20	Ile Asn	Ala	Leu Ser	Asn	Ser	Leu	Leu	Arg	His	His	Asn	Met	Val	Tyr
	:	1635			1	.640				1	L645			
	Ala Thr	Thr	Ser Arg	Ser	Ala	Gly	Leu	Arg	Gln	Lys	Lys	Val	Thr	Phe
	1650				L655					1660				
	Asp Arg	Leu	Gln Val	Leu	Asp	Asp	His	Tyr	Arg	Asp	Val	Leu	Lys	Glu
25	1665			1670					.675					1680
	Met Lys	Ala		Ser	Thr	Val			Lys	Leu	Leu			Glu
			1685					690					695	
	Glu Ala	_	_	Thr	Pro			Ser	Ala	Lys		-	Phe	Gly
2.0			700		_		705			_		710		
30	Tyr Gly		Lys Asp	Val	-		Leu	Ser	Ser	-		Val	Asn	His
		1715		_		720	_				1725	,	_	
	Ile His	Ser	Val Trp	-	-	Leu	Leu	Glu	-		Va⊥	Thr	Pro	Ile
	1730	<b>™</b> ~	Tlo Mot		1735	7	C1	17-1		.740	3703	C1 ~	Dwa	C1
35	Asp Thr	IIIE		A1a 1750	rλa	ASII	GIU		755.	cys	val	GIN		
,,	1745 Lys Gly	GI v			<b>Δ</b> 1 ⇒	Δτα	T. 211			Dha	Pro	Aen		.760
	mas era	эту.	1765	<u> </u>	nia.	nry		770	4 CT	£116	- 10	_	775	ату

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	Val Ar	g Val	L Cys	Glu	Lys	Met	Ala	Leu	Туг	Asp	Val	Val	Ser	Thr	Leu
			1780					1785					1790	ı	
	Pro Gli	n Val	. Val	Met	Giy	Ser	: Ser	Tyr	Gly	Phe	Gln	Tyr	Ser	Pro	Gly
5		1795	<b>;</b>				1800	l				1805			
	Gln Arg	y Val	. Glu	Phe	Leu	Val	. Asn	Thr	Trp	Lys	Ser	Lys	Lys	Asn	Pro
	1810	)				1815	5				1820				
	Met Gl	, Phe	Ser	Tyr	Asp	Thr	Arg	Cys	Phe	Asp	Ser	Thr	Val	Thr	Glu
	1825				1830					1835					1840
10	Asn Asp	) Ile	Arg	Val	Glu	Glu	Ser	Ile	Tyr	Gln	Cys	Cys	Asp	Leu	Ala
			:	1845				:	1850					1855	
	Pro Glu	Ala	Arg	Gln	Ala	Ile	Lys	Ser	Leu	Thr	Glu	Arg	Leu	Tyr	Ile
			1860					1865					1870		
	Gly Gly			Thr	Asn	Ser	Lys	Gly	Gln	Asn	Cys	Gly	Tyr	Arg	Arg
15		1875					1880					1885			
	Cys Arg		Ser	Gly	Val	Leu	Thr	Thr	Ser	Cys	Gly	Asn	Thr	Leu	Thr
	1890					1895					1900				
	Cys Tyr	Leu	Lys			Ala	Ala	Cys	Arg	Ala	Ala	Lys	Leu	Gln	Asp
20	1905		_		1910					1915					1920
20	Cys Thr	Met			Asn	Gly	Asp			Val	Val	Ile	Cys	Glu	Ser
	71 n Cl.	. m		1925	_				.930					935	
	Ala Gly		Gin 1940	GIu	Asp	Ala			Leu	Arg	Val			Glu	Ala
	Met Thr			e	71-	D		1945		_	_		950		
25	Met Thr	1955	ıyı	Ser	Ala		1960	GIŸ	Asp	Pro			Pro	Glu	Tyr
	Asp Leu		ī.eu	Tle	<b>ጥ</b> ክ ድ			502	502	7.00		.965	17-1	<b>7</b> .1 -	***
	1970					.975	uy.	Jer	Ser		.980	Ser	vaı	ATA	uis
	Asp Ala	Ser	Glv	Lvs			Tvr	Tvr	Leu			Asn	Pro	ሞክ ፦	Th ≻
	1985		-		.990		- 4 -	-1-		.995	9	• р			000
30	Pro Leu	Ala	Arg	Ala	Ala	Trp	Glu	Thr			His	Thr	Pro		
				005		-			010					015	
	Ser Trp	Leu	Gly	Asn	Ile	Ile	Met	Tyr .	Ala	Pro	Thr	Leu			Arg
			2020					025					030		•
	Met Ile	Leu	Met	Thr	His	Phe	Phe	Ser	Ile	Leu	Leu	Ala	Gln	Glu	Gln
35	:	2035				2	2040				2	045			
	Leu Glu	Lys	Ala	Leu	Asp	Cys	Gln	Ile	Tyr	Gly	Ala	Cys	Tyr	Ser	Ile
	2050				2	055				2	060				

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	Glu Pr	o Leu	Asp Let	Pro	Gln	Ile	Ile	Glu	Arg	Leu	His	Gly	Leu	Ser
	2065			2070				:	2075				;	2080
	Ala Ph	e Ser	Leu His	Ser	Tyr	Ser	Pro	Gly	Glu	Ile	Asn	Arg	Val	Ala
5			2085	i			:	2090				:	2095	
	Ser Cy	s Leu	Arg Lys	Leu	Gly	Val	Pro	Pro	Leu	Arg	Val	Trp	Arg	His
		2	2100			2	2105					2110		
	Arg Ala	a Arg	Ser Val	Arg	Ala	Arg	Leu	Leu	Ser	Gln	Gly	Gly	Arg	Ala
		2115			2	2120				2	2125			
10	Ala Th	r Cys	Gly Lys	Tyr	Leu	Phe	Asn	Trp	Ala	Val	Lys	Thr	Lys	Leu
	213	כ		:	2135				:	2140				
	Lys Le	ı Thr	Pro Ile	Pro	Ala	Ala	Ser	Arg	Leu	Asp	Leu	Ser	Gly	Trp
	2145			2150				2	2155				2	2160
	Phe Val	L Ala	Gly Tyr	Ser	Gly	Gly	Asp	Ile	Tyr	His	Ser	Leu	Ser	Arg
15			2165				2	2170				2	2175	
	Ala Arq	g Pro	Arg Trp	Phe	Met	Leu	Cys	Leu	Leu	Leu	Leu	Ser	Val	Gly
		2	180			2	2185				2	2190		
	Val Gly	, Ile	Tyr Leu	Leu	Pro	Asn	Arg							
		2195			2	200								
20														
	(3)		ORMAT]											
		(i)		UENC										
				LENG						25				
25				TYPE				-						
25				STRA					gre					
		(ii		TOPO					a+ i a	- T\XI	·7\			
		•	.i) HYP	ECUL			. sy No		ELTC	. DIN	A			
		(iv		ISEN			NO	r						
30		•	i) IMM				ነርፑ•	01	i aor	11107	ent:	i da		
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		(ix	:) FEA											
		(		NAME		liac	a							
				IDEN		_		ME'	THOL	); P	olva	acrv	'lam	ide
35			gel							-	- 4	- 1		
		(xi	.) SEQ	UENC	E DE	ESCF	RIPT	ION	: SE	Q I	D NO	): 3		

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GCCGAGATGC CATCTTCAAA CAGTTC

	7.45	T117701		
	(4)		RMATION FOR SEQ ID NO: 4	
5		(i)		
S			(A) LENGTH: 24 nucleotides	
			(B) TYPE: nucleic acid	
			(C)STRANDEDNESS: single	
			(D) TOPOLOGY: linear	
			MOLECULE TYPE: synthetic DNA	
10		(iii)	HYPOTHETICAL: No	
			ANTISENSE: No	
		(vii)	IMMEDIATE SOURCE: oligonucleotide	
			synthesizer	
		(ix)	FEATURE:	
15			(A) NAME: oligo b	
			(C) IDENTIFICATION METHOD: Polyacrylamide	
			gel	
		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 4	
20	GTGTACA	ACA A	GGTCCATAT CACC	24
	(5)	INFOR	MATION FOR SEQ ID NO: 5	
		(i)	SEQUENCE CHARACTERISTICS	
			(A) LENGTH: 24 nucleotides	
25			(B) TYPE: nucleic acid	
			(C)STRANDEDNESS: single	
			(D) TOPOLOGY: linear	
		(ii)	MOLECULE TYPE: synthetic DNA	
		(iii)	HYPOTHETICAL: No	
30		(iv)	ANTISENSE: No	
		(vii)	IMMEDIATE SOURCE: oligonucleotide	
			synthesizer	
		(ix)	FEATURE:	
			(A) NAME: oligo c	
35			(C) IDENTIFICATION METHOD: Polyacrylamide	
			gel	
		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 5	

GGTCTTTCTG AACGGGATAT AAAC

24

	(6)	INFO	RMATION FOR SEQ ID NO: 6:	
5		(i)	SEQUENCE CHARACTERISTICS	
			(A) LENGTH: 31 nucleotides	
			(B) TYPE: nucleic acid	
			(C)STRANDEDNESS: single	
			(D) TOPOLOGY: linear	
10		(ii)	MOLECULE TYPE: synthetic DNA	
			HYPOTHETICAL: No	
			ANTISENSE: No	
			IMMEDIATE SOURCE: oligonucleotide	
			synthesizer	
15		(ix)	FEATURE:	
			(A) NAME: 5'-5B	
			(C) IDENTIFICATION METHOD: Polyacrylamide	
			gel	
		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 6	
20			•	
	AAGGAT	CCAT G	TCAATGTCC TACACATGGA C	31
	(7)	INFOR	MATION FOR SEQ ID NO: 7:	
		(i)	SEQUENCE CHARACTERISTICS	
25			(A) LENGTH: 36 nucleotides	
			(B) TYPE: nucleic acid	
			(C)STRANDEDNESS: single	
			(D) TOPOLOGY: linear	
		(ii)	MOLECULE TYPE: synthetic DNA	
30			HYPOTHETICAL: No	
		(iv)	ANTISENSE: Yes	
		(vii)	IMMEDIATE SOURCE: oligonucleotide	
			synthesizer	
		(ix)	FEATURE:	
35			(A) NAME: 3'-5B	
			(C) IDENTIFICATION METHOD: Polyacrylamide	
			go.]	

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7

	AATATT	CGAA T'	CATCGGTT GGGGAGCAGG TAGATG	36
5	(8)	INFOR	MATION FOR SEQ ID NO: 8:	
		(i)	SEQUENCE CHARACTERISTICS	
			(A) LENGTH: 22 nucleotides	
			(B) TYPE: nucleic acid	
			(C)STRANDEDNESS: single	
10			(D) TOPOLOGY: linear	
		(ii)	MOLECULE TYPE: synthetic DNA	
		(iii)	HYPOTHETICAL: No	
		(iv)	ANTISENSE: No	
		(vii)	IMMEDIATE SOURCE: oligonucleotide	
15			synthesizer	
		(ix)	FEATURE:	
			(A) NAME: Dpr1	
			(C) IDENTIFICATION METHOD: Polyacrylamid	е
			gel	
20		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 8	
	TGGCTG	GCAA G	GCACACAGG CT 22	
	(9)	INFOR	MATION FOR SEQ ID NO: 9	
25		(i)	SEQUENCE CHARACTERISTICS	
			(A) LENGTH: 20 nucleotides	
			(B) TYPE: nucleic acid	
			(C)STRANDEDNESS: single	
			(D) TOPOLOGY: linear	
30		(ii)	MOLECULE TYPE: synthetic DNA	
		(iii)	HYPOTHETICAL: No	
		(iv)	ANTISENSE: Yes	
		(vii)	IMMEDIATE SOURCE: oligonucleotide	
			synthesizer	
35		(ix)	FEATURE:	
			(A) NAME: Dpr2	

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(C) IDENTIFICATION METHOD: Polyacrylamide

			gel	
		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 9	
5	AGGCA	GGGTA G	SATCTATGTC	20
	(10)	INFOR	RMATION FOR SEQ ID NO: 10	
		(i)	SEQUENCE CHARACTERISTICS	
			(A) LENGTH: 20 nucleotides	
10			(B) TYPE: nucleic acid	
			(C)STRANDEDNESS: single	
			(D) TOPOLOGY: linear	
		(ii)	MOLECULE TYPE: synthetic DNA	
		(iii)	HYPOTHETICAL: No	
15		(iv)	ANTISENSE: No	
		(vii)	IMMEDIATE SOURCE: oligonucleotide	
			synthesizer	
		(ix)	FEATURE:	
			(A) NAME: NS5B-5'(1)	
20			(C) IDENTIFICATION METHOD: Polyacrylamide	
			gel	
		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 10	
25	TCAATG	TCCT A	CACATGGAC	20
	(11)	INFOR	MATION FOR SEQ ID NO: 11	
		(i)	SEQUENCE CHARACTERISTICS	
			(A) LENGTH: 38 nucleotides	
			(B) TYPE: nucleic acid	
30			(C)STRANDEDNESS: single	
			(D) TOPOLOGY: linear	
		(ii)	MOLECULE TYPE: synthetic DNA	
		(iii)	HYPOTHETICAL: No	
		(iv)	ANTISENSE: Yes	
35		(vii)	IMMEDIATE SOURCE: oligonucleotide	
			synthesizer	
		(ix)	FEATURE:	

399

		(A) NAME: HCVA-13	
		(C) IDENTIFICATION METHOD: Polyacrylamide	
		gel	
	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 11	
5			
	GATCTCTAGA T	CATCGGTTG GGGGAGGAGG TAGATGCC	38
	(12) INFOR	MATION FOR SEQ ID NO: 12	
	(i)	SEQUENCE CHARACTERISTICS	
10		(A) LENGTH: 399 nucleotides	
		(B) TYPE: nucleic acid	
		(C)STRANDEDNESS: single	
		(D) TOPOLOGY: linear	
	(ii)	MOLECULE TYPE: mRNA	
15	(iii)	HYPOTHETICAL: No	
	(iv)	ANTISENSE: No	
	(vi)	ORIGINAL SOURCE:	
		(A) ORGANISM: Rattus Norvegicus	
		(B)STRAIN : Sprague-Dawley	
20	(vii)	IMMEDIATE SOURCE: pT7-7 (DCoH)	
	(ix)	FEATURE:	
		(A) NAME: D-RNA	
		(C) IDENTIFICATION METHOD: Polyacrylamide	
		gel	
25	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 12	
	GGGAGACCAC AAC	eguuucc cucuagaaau aauuuuguuu aacuuuaaga aggagauaua	4 6
	CAUAUGGCUA GAAI	JUCGCGC CCUGGCUGGC AAGGCACACA GGCUGAGUGC UGAGGAACGC	- 12
	GACCAGCUGC UGC	CAAACCU GCGGGCCGUG GGGUGGAAUG AACUGGAAGG CCGAGAUGCC	: 18
30	AUCUUCAAAC AGUI	JCCAUUU UAAAGACUUC AACAGGGCUU UUGGCUUCAU GACAAGAGU	24
	GCCCUGCAGG CUG	AAAAGCU GGACCACCAU CCCGAGUGGU UUAACGUGUA CAACAAGGU	30

## SUBSTITUTE SHEET (RULE 26)

AGCUUCAUCG AACAAGUUGC CGUGUCUAUG ACAUAGAUC

CAUAUCACCU UGAGCACCCA CGAAUGUGCC GGUCUUUCUG AACGGGAUAU AAACCUGGCC 360

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	(13)	INFORMATI	ON FOR SEQ ID NO: 13:	
	(i)	SEQUENCE	CHARACTERISTICS	
		(A)	LENGTH: 20 nucleotides	
		(B)	TYPE: nucleic acid	
5		(C)	STRANDEDNESS: single	
		(D)	TOPOLOGY: linear	
		(ii) MOLE	CULE TYPE: synthetic DNA	
		(iii) HYPC	THETICAL: No	
		(iv) ANTI	SENSE: No	
10		(vii) IMME	DIATE SOURCE: oligonucleotide synthesiz	er
		(ix) FEAT	URE:	
		(A)	NAME: NS5B-up	
		(C)	IDENTIFICATION METHOD: Polyacrylamide	gel
		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 13	
15				
	TGTC	AATGTC CTA	CACATGG	20
	(14)		ON FOR SEQ ID NO: 14:	
			ENCE CHARACTERISTICS	
20		• •	LENGTH: 38 nucleotides	
			TYPE: nucleic acid	
			STRANDEDNESS: single	
		• •	TOPOLOGY: linear	
			CULE TYPE: synthetic DNA	
25		•	THETICAL: No	
			SENSE: Yes	
			DIATE SOURCE: oligonucleotide synthesiz	er
		(ix) FEAT		
			NAME: 3'-5B	_
30			IDENTIFICATION METHOD: Polyacrylamide	gel
,		(xi)	SEQUENCE DESCRIPTION: SEQ ID NO: 14	
	AATA:	ITCGAA TTC	ATCGGTT GGGGAGCAGG TAGATG	36